DETAILED ACTION

Claims 1-17 are pending. Claims 1-12 and 16 are under consideration in the instant office action.

Claims 13-15 and 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claims. Applicants' response to the restriction/species election requirements submitted on 7/22/2008 is acknowledged and has been considered.

Election/Restrictions

Applicant's election of Group I in the reply filed on 7/22/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In addition, examiner acknowledges an error in the office action mailed 05/22/08 for requirement for restriction/election on the grouping of the inventions and corrected it as follows:

Group I, claims 1-12 and 16 drawn to antisolvent solidification process and method of using the process for the preparation of pharmaceutical dosage form;

Group II, claims 13-15 and 17 drawn to crystalline particles and method of using crystalline particles.

In accordance with the September 23, 2008 telephone discussion with the attorney applicants' election of the species of saccharides as the organic or inorganic compound type and 3-ketodesogestrel as the pharmaceutical compound type is also acknowledged. Examiner also

acknowledges that the species election for the pharmaceutical compound type is expanded to progesterone.

Priority

The earliest effective filing date afforded for the instantly claimed invention, has been determined to be 04/29/2003, the filing date of the provisional application 60/466,761.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 01/20/2006, 01/27/2006, and 09/02/2008 was noted and the submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the examiner has considered the information disclosure statement.

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Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Since the method does not recite any particular step, it is unclear what is meant by "using the process". It is unclear to one of ordinary skilled in the art what steps are involved in the claimed method.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness

Claims 1-3, 5-8, 10 and 16, are rejected under 35 U.S.C. 103(a) as being unpatentable over Jakupovic et al. (US Patent No. 6,221,398, IDS reference).

Applicant Claims

Applicant claims an antisolvent solidification process for preparing a solid composition comprising at least one organic or inorganic compound, wherein a liquid medium comprising at least one dissolved organic or inorganic compound is forced through a membrane which is positioned in a membrane module into one or more antisolvents or wherein one or more antisolvents are forced through a membrane which is positioned in a membrane module into a liquid medium comprising at least one organic or inorganic compound, and whereby the process is carried out as a continuous process, yielding a composition comprising solid particles comprising said organic and/or inorganic compound(s). In other embodiments, instant claim 2 recites a process wherein the solidification is a crystallisation, the prepared solid particles are crystalline particles, the organic or inorganic compound is a crystallisable compound, and, optionally, said crystalline particles are recovered from the process. Instant claim 3 recites a process as recited in claim 1 wherein the liquid medium is separated from the one or more antisolvents by means of nanofiltration and wherein, optionally, the liquid medium and/or the antisolvent(s) is/are recycled. Instant claim 5 recites a process as recited in instant claim 1 wherein a nonsolvent is present in the liquid medium and/or in the one or more antisolvent. Instant claim 6 recites a process as recited in instant claim 1, wherein the organic or inorganic compound is a saccharide as per applicant's species election. Instant claim 7 recites a process as recited in claim 1 wherein the solid particles essentially consist of particles of only one inorganic or organic compound. Instant claim 8 recites a process as recited in instant claim 1 wherein the inorganic or organic compound is a pharmaceutical compound. Instant claim 10 recites a process as recited in claim 1 wherein the solid composition comprises a mixture of two or more

pharmaceutical compounds. Instant claim 16 recites a method of using the process recited in instant claim 1 in the preparation of a pharmaceutical dosage form.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Jakupovic et al. teach a process for producing a pharmaceutical powder for inhalation comprising crystalline particles of an inhalation compound, comprising dissolving an inhalation compound to be provided in crystalline particle form in a solvent; and introducing the solution containing the inhalation compound, in droplet form or as a jet stream into an anti-solvent which is miscible with the solvent and which is under agitation, under non-supercritical conditions (column 2, lines 26-34). Jakupovic et al. disclose that once the compound is dissolved the solution is preferably added to the antisolvent through **a porous filter** having pores of 10-160 microns (column 4, lines 24-27). This teaching reads on the limitation reciting forcing the liquid medium through a membrane.

Jakupovic et al. disclose an illustrative example where a solution of budesonide in methanol was added to water/ice at a rate of 1 ml/min, through a glass filter with a porosity of 40-90 microns, and with stirring with ultraturrax equipment. The obtained slurry contained **budesonide** crystalline particles of MMD 2.79 microns. 90% of the particles had a diameter of below 6.0 μm (column 5, lines 20-26, example 2).

Jakupovic et al. disclose a list of medically useful compounds which may be provided in respirable particle form such as β2-adrenoteceptor agonists, glucocorticosteroids like budesonide etc (column 3, lines 8-32). Jakupovic et al. disclose the process may be used to prepare **carbohydrates (saccharides)** such as lactose, dextrose, melezitose, maltose, mannitol, trehalose

and raffinose, as well as salts of fatty acids, bile salts, phospholipids and alkyl glycosides, which may be useful as penetration enhancers (column 3, lines 45-50). Furthermore, Jakupovic et al. disclose the pharmaceutically acceptable additive may be prepared in the same manner as the medically useful compound, and the powders may then be mixed together, or a powder containing the medically useful compound and additive may be prepared in certain cases, i.e. when the compound and additive have similar solubilities, by dissolving all of the desired substances together in the solvent (column 3, lines 50-57).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Jakupovic et al. is silent whether the process is continuous or not.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made in general to produce the instant invention, because Jakupovic et al. taught a similar process for the preparation of solid crystal particles following the steps recited in the instant claimed invention. The skilled artisan would have been motivated to follow a process of solidification of organic or inorganic compounds using the solvent/antisolvent system as recited in the instant invention, because the claimed process is well known in the art as a method which is useful for the preparation of solid crystal particles. With regard to the limitation reciting the process being continuous, the skilled artisan would have been motivated to make the process continuous because a continuous process will result in a more efficient chemical manufacture,

delivering lower raw material and waste cost, and reducing environmental emissions, energy consumption and unit process operations resulting in products with high yield and of better quality. However, in a large scale production the versatility and simplicity of operating batch based glass wares and vessels is quite difficult. Additionally, batch processes have to be run under optimum conditions such as high dilution and low temperatures to overcome exothermic reaction conditions or to accomplish particular product selectivity. Furthermore, it is with in the purview of the skilled artisan to modify a process from a given batch process to achieve a continuous process (MPEP 2144.04).

A skilled artisan would have had a reasonable expectation of success because Jakupovic et al. addresses a process of solidification of pharmaceutical compounds through the formation of solid crystal particles. In light of the forgoing discussion, one of ordinary skill in the art would have concluded that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the reference, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the reference, especially in the absence of evidence to the contrary.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jakupovic et al. (US Patent No. 6,221,398) as applied to claims 1-3, 5-8, 10, and 16 above, and further in view of Nocent et al., *J. Pharm. Sci*, 90, 1620-1627.

Applicant Claims

Applicants claim a method as described above, wherein an emulsion is formed before said composition comprising solid particles is obtained.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

As discussed above the required limitations of instant claim 1 are addressed by the teachings of Jakupovic et al.

Nocent et al. disclose quasi-emulsion solvent diffusion method where "the drug is dissolved in solvent and the antisolvent phase (antisolvent and emulsifier) are prepared separately and maintained at different temperatures. Nocent et al. also disclose that the crystallization process incorporating the emulsifier is attractive because it can lead to significant improvements in the physical properties of materials, such as flowability, compressibility and compactibility (see page 1620). The solvent solution is then added to the antisolvent solution under agitation. Since interactions between drug and solvent being stronger than the interactions between solvent and antisolvent, the solvent is dispersed in the antisolvent and creates a quasi-emulsion. The formation of this unstable emulsion is induced by the increase in the interfacial tension between solvent and antisolvent. However, since emulsifier is added the emulsion is formed resulting in the solvent and antisolvent diffusing in opposite directions, specially the antisolvent diffusing into the droplets, reducing the solubility of the drug and inducing crystallization inside the droplets" (see page 1621).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Jakupovic et al. does not explicitly teach a process of forming an emulsion before solid particles are formed. This deficiency is cured by the teachings of Nocent et al.

Finding of Prima Facie Obviousness Rationale and Motivation
(MPEP §2142-2143)

It would have been prima facie obvious to a person of ordinary skill in the art at the time of the instant invention to modify the teachings of Jakupovic via the formation of an emulsion, because Nocent teaches a similar process of crystallization where a drug is dissolved in solvent and added to the antisolvent in the presence of an emulsifier to form an emulsion resulting in crystal particles of the drug. An ordinary skilled artisan would have been motivated to combine the teachings of Jakupovic and Nocent, because Jakupovic teaches a process of solidification of chemical compounds by dissolving the compound in solvent and passing it through a porous filter (membrane) and adding it to antisolvent for forming solid crystal particles and Nocent teaches a similar process of crystallization where a drug is dissolved in solvent and added to the antisolvent in the presence of an emulsifier to form an emulsion resulting in crystal particles of the drug. Thus, an ordinary skilled artisan would have had a reasonable expectation of success upon combination of the prior art teachings, because both references teach similar processes of crystallization of chemical compounds using the solvent/antisolvent system, specifically, Nocent's process utilizing the addition of an emulsifier demonstrated to be useful during the crystallization process to form a stable emulsion form from the unstable quasi-emulsion formed

as a result of interactions between drug and solvent being stronger than the interactions between solvent and antisolvent (see page 1621).

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jakupovic et al. (US Patent No. 6,221,398) as applied to claims 1-3, 5-8, 10, and 16 above, and further in view of Chen et al. (US Patent No 7,374,779) as evidenced by Nakagawa et al. (Japan J. Pharmacol. 29, 509-514, 1979)..

Applicant Claims

Applicants claim a method as described above, wherein the inorganic or organic pharmaceutical compound is 3-ketodesogestrel as per applicant's species election. Examiner also acknowledges that the species election for the pharmaceutical compound type is expanded to progesterone too.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

As discussed above the required limitations of instant claim 1 are addressed by the teachings of Jakupovic et al..

Chen et al. disclose a novel pharmaceutical formulation that provides for increased absorption and bioavailability of active agents, particularly active agents that are administered orally (column 8, lines 58-61). Chen et al. disclose a list of active agents that includes preferred sex hormones such as progestins, such as **,3-ketodesogestrel** (column 10, line 24).

Chen et al. disclose that the active agent can be dissolved in appropriate solvent and subjected to crystallization (column 54, lines 35-37 and claim 8) via precipitation by antisolvent (column 54, lines 50-54).

Chen et al. disclose an illustrative example of a pharmaceutical formulation comprising **progesterone** (column 73, example 48).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Jakupovic et al. does not explicitly teach of a process of forming **progesterone** or **3-ketodesogestrel** crystal particles. This deficiency is cured by the teachings of Chen et al.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Jakupovic et al. and Chen et al., because as discussed above Chen teaches that the active agent can be dissolved in appropriate solvent and subjected to crystallization via precipitation by antisolvent to form pharmaceutical solid particles of **3-ketodesogestrel** or progesterone. Moreover, one of ordinary skill in the art would also recognize that substituting one anti-inflammatory agent such as progesterone as evidenced by Nakagawa et al. for another (e.g. budesonide) is obvious because the selection of a known material based on its suitability for its intended use supports a determination of *prima facie* obviousness (MPEP § 2144.07). A skilled artisan would have had a reasonable expectation of

success because the anti-inflammatory agents will serve the same intended function healing inflammation after being crystallized through the same process.

Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jakupovic et al. (US Patent No. 6,221,398) as applied to claim 1-3, 5-8, 10, and 16 above, and further in view of Maruyama et al. (US Patent No 5,512,092).

Applicant Claims

Applicants claim a method as described above, wherein the solid particles are coated with a coating solution.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

As discussed above the required limitations of instant claim 1 is made obvious by the teachings of Jakupovic et al..

Maruyama et al. disclose a method for preparing an aqueous emulsion for coating solid pharmaceutical preparations comprising the steps of dissolving a cellulosic polymer in a mixed solvent of water and an organic solvent capable of being admixed with water in any rate to give a polymer solution, self-emulsifying the polymer solution by mixing with water and then concentrating the resulting emulsified stock solution. The concentration is carried out by removing a part of the liquid components while passing it through a membrane for ultrafiltration until the polymer concentration of the resulting emulsion reaches a level of not less than 7% by weight (see Abstract).

Maruyama et al. disclose the coating treatment is performed by spraying to the solid particles (column 4, line 21).

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Jakupovic et al. does not teach of a process of coating the solid particles, which are formed via the above discussed process, by passing a liquid medium comprising dissolved coating material through a membrane into a suspension of particles. This deficiency is cured by the teachings of Maruyama et al.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Jakupovic et al. by coating the solid particles, because, Maruyama as discussed above teaches coating pharmaceutical solids utilizing drug coating materials. One of ordinary skilled in the art would be motivated to do the coating because it will serve not only protect a drug having low resistance to acids from the attack thereof in the stomach, but also protect the gastric mucous membrane from the attack of the drug which may stimulate and damage the wall of the stomach and is dissolved after the arrival at the intestines wherein the pharmaceutical preparation shows its desired pharmacological action as described by Maruyama et al. With regard to passing the coating solution through a membrane one of ordinary skilled in the art would be motivated to do that, because the step would help to concentrate and adjust the concentration of the coating solution to a needed level as also

demonstrated by Maruyama et al.. A skilled artisan would have had a reasonable expectation of success because both Jakupovic et al. and Maruyama et al. are concerned with pharmaceutical solid particles.

Conclusion

Claims 1-12 and 16 are pending, while claims 13-15 and 17 are withdrawn. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIGABU KASSA whose telephone number is (571)270-5867. The examiner can normally be reached on 9 am-5 pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Tigabu Kassa 9/26/08

/Mina Haghighatian/
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